NDA 11-178/S-037

SEP 3 0 1998

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016-1389

Attention: Kimberly Lampasona
Manager
Drug Regulatory Affairs

Dear Ms. Lampasona:

Please refer to your supplemental new drug application dated April 3, 1998, received April 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isuprel (isoproterenol hydrochloride inhalation aerosol).

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for labeling that reflect the revised target medication delivery.

We have completed our review of this supplemental application and it is approved, effective as of the date of this letter. We remind you of your commitment to respond to labeling comments forwarded to you for supplement S-035.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, patient package insert, and immediate container and carton labels submitted April 3, 1998).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 1 1-178/S-037." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ISUPREL®

ISOPROTERENOL HYDROCHLORIDE INHALATION AEROSOL, USP

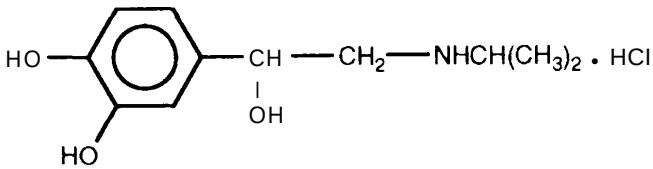
In MISTOMETER

Oral Inhaler

DESCRIPTION

ISUPREL, isoproterenol hydrochloride, is a beta agonist sympathomimetic bronchodilator. MISTOMETER is a complete nebulizing unit consisting of a plastic-coated glass vial of aerosol solution, detachable plastic mouthpiece with built-in nebulizer, and protective cap. The vial contains isoproterenol hydrochloride 0.25% (w/w) with inert ingredients of alcohol 33% (w/w) and ascorbic acid 0.1% (w/w) and, as propellants, dichlorodifluoromethane and dichlorotetrafluoroethane.

Isoproterenol hydrochloride is a racemic compound with a molecular weight of 247.72 and a molecular formula $C_{11}H_{17}NO_3 \cdot HCl$. Chemically, isoproterenol hydrochloride is 3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol hydrochloride and has the following structural formula:



The contents permit the delivery of not less than 200 actuations from the 11.2 g (10 mL) vial and not less than 300 actuations from the 16.8 (15 mL) vial. The MISTOMETER delivers a measured dose of 103 mcg of the bronchodilator in a fine, even mist for inhalation.

CLINICAL PHARMACOLOGY

ISUPREL relaxes bronchial spasm and facilitates expectoration of pulmonary secretions by acting almost exclusively on beta receptors. It is frequently effective when epinephrine and other drugs fail, and it

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has a wide margin of safety.
ISUPREL is readily absorbed when given as an aerosol. It is metabolized primarily in the liver and other tissues by catechol-O-methyltransferase (COMT).

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were concomitantly administered. The significance of these findings when applied to human usage is currently unknown.

INDICATIONS AND USAGE

ISUPREL is indicated for the relief of bronchospasm associated with acute and chronic asthma and reversible bronchospasm which may be associated with chronic bronchitis or emphysema.

CONTRAINDICATIONS

Use of isoproterenol in patients with preexisting cardiac arrhythmias associated with tachycardia is generally considered contraindicated because the cardiac stimulant effect of the drug may aggravate such disorders. The use of this medication is contraindicated in those patients who have a known hypersensitivity to isoproterenol or to any of the other components of this drug.

WARNINGS

Excessive use of an adrenergic aerosol should be discouraged as it may lose its effectiveness.

In patients with status asthmaticus and abnormal blood gas tensions, improvement in vital capacity and in blood gas tensions may not accompany apparent relief of bronchospasm. Facilities for administering oxygen mixtures and ventilatory assistance are necessary for such patients

Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

ISUPREL- isoproterenol hydrochloride inhalation aerosol

Deaths have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances,

PRECAUTIONS

General

Isoproterenol should be used with caution in patients with cardiovascular disorders including coronary insufficiency, diabetes, or hyperthyroidism, and in persons sensitive to sympathomimetic amines.

A single treatment with the ISUPREL MISTOMETER is usually sufficient for controlling isolated attacks of asthma. Any patient who requires more than three aerosol treatments within a 24-hour period should be under the close supervision of a physician. Further therapy with the ronchodilator aerosol alone is inadvisable when three to five treatments within six to twelve hours produce minimal or no relief.

Information for Patients

Do not inhale more often than directed by your physician. Read enclosed instructions before using (see attachment to insert). Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately. Avoid spraying in eyes. Contents under pressure. Do not break or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children.

Drug Interactions

Epinephrine should not be administered concomitantly with ISUPREL, as both drugs are direct cardiac stimulants and their combined effects may induce serious arrhythmia. If desired they may, however, be alternated, provided an interval of at least four hours has elapsed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term chronic toxicity studies in animals have not been done to evaluate isoproterenol in these areas.

Pregnancy Category C

Animal reproduction studies have not been conducted with isoproterenol hydrochloride. It is also not known whether isoproterenol hydrochloride can

cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Isoproterenol hydrochloride should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoproterenol hydrochloride is administered to a nursing woman.

Pediatric Use

In General, the technique of ISUPREL MIST0METER in administration to children is similar to that of adults, since children's smaller ventilatory exchange capacity automatically provides proportionally smaller aerosol intake.

ADVERSE REACTIONS

The mist from the ISUPREL MISTOMETER contains alcohol but is generally very well tolerated. An occasional patient may experience some transient throat irritation which has been attributed to the alcohol content.

Serious reactions to ISUPREL are infrequent. The following reactions, however, have been reported:

CNS: Nervousness, headache, dizziness, weakness.

Gastrointestinal: Nausea, vomiting.

Cardiovascular: Tachycardia, palpitations, precordial distress, anginal-type pain.

Other: Flushing of the skin, tremor, and sweating.

The inhalation route is usually accompanied by a minimum of side effects. These untoward reactions disappear quickly and do not as a rule, inconvenience the patient to the extent that the drug must be discontinued. No cumulative effects have been reported

OVERDOSAGE

Overdosage of ISUPREL may produce signs and symptoms typical of excessive sympathomimetic effects, including tachycardia, palpitations, nervousness, nausea, and vomiting. Excessive use of adrenergic aerosols ma result in loss of effectiveness or severe paradoxical airway resistance. Cardiac arrest has been noted in several instances.

In all cases of overdose or excessive use of ISUPREL, the drug should be discontinued immediately and vital functions supported until the patient is stabilized. It is not known whether isoproterenol hydrochloride is diatyzable.

The acute oral LD_{50} in mice is 3,850 mg/kg ± 1 ,190 mg/kg of pure drug in solution (isoproterenol hydrochloride). In dogs, the toxic dose is 1,000 times the therapeutic dose. Converted to the amount used clinically in man, this would be about 2,500 times the therapeutic dose.

DOSAGE AND ADMINISTRATION

Acute Bronchial Asthma; Hold the MISTOMETER in an inverted position. Close lips and teeth around open end of mouthpiece. Breathe out, expelling as much air from the lungs as possible; then inhale deeply while pressing down on the bottle to activate spray mechanism. Try to hold breath for a few seconds before exhaling. Wait one full minute in order to determine the effect before considering a second inhalation. A treatment may be repeated up to 5 times daily if necessary. (See **PRECAUTIONS:** If carefully instructed,children quickly learn to keep the stream of mist clear of the teeth and tongue, thereby assuring inhalation into the lungs. Occlusion of the nares of very young children may be advisable to make inhalation certain.

Warm water should be run through the mouthpiece once daily to wash it and prevent clogging.

The mouthpiece may also be sanitized by immersion in alcohol.

Bronchospasm in Chronic Obstructive Lung Disease:The MISTOMETER provides a convenient aerosol method for delivering ISUPREL. The treatment described above for Acute Bronchial Asthma may be repeated at not less than 3 to 4 hour intervals as part of a programmed regimen of treatment of obstructive lung disease complicated by a reversible bronchospastic component. One application from the MISTOMETER may be regarded as equivalent in effectiveness to 5 to 7 operations of a hand-bulb nebulizer using a 1 :100 solution.

Pediatric Dosage

In general, the technique of ISUPREL MIST0METER in administration to children is similar

to that of adults, since children's smaller ventilatory exchange capacity automatically provides proportionally smaller aerosol intake.

HOW SUPPLIED

ISUPREL MISTOMETER is supplied in a plastic coated glass vial as a metered dose aerosol providing 103 mcg of isoproterenol hydrochloride per actuation. There are 200 actuations per 10 mL.

Vial of 16.8 g (15 mL) with oral nebulizer (NDC 0024-0878-01)

Refill only, 16.8 g (15 mL) (NDC 0024-0879-01)

Store at room temperature up to 30°C(86° F).

Caution: Federal law prohibits dispensing without prescription.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

WARNING: Contains dichlorodifluoromethane and dichlorotetrafluoroethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

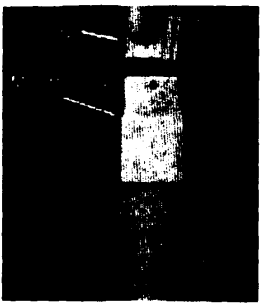
A notice similar to the above WARNING has been placed in the information for the patient of this product pursuant to EPA regulations.

sanofi

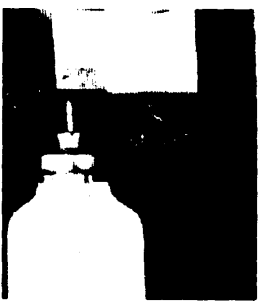
Manufactured for
Sanofi Pharmaceuticals, Inc.
New York, NY 10016
by Nycomed Puerto Rico Inc.
Barceloneta, Puerto Rico 00617

Revised December 1997

DIRECTIONS FOR USE OF MISTOMETER



1 Pull cap from mouthpiece.



2 Pull mouthpiece off bottle, turn it sideways, and fit hole in flattened end onto metal spout (valve stem) of bottle.

3 Hold assembled unit between thumb and index finger. Invert bottle and dose lips and teeth around open end of mouthpiece. During use, the Mistometer must always be inverted as it does not operate properly in an upright position. Run warm water through mouthpiece once daily to wash it and prevent clogging. You may sanitize it by immersing it in alcohol. Hold bottle before light to determine volume of contents.

See over for steps 4 and 5

4 Breathe out, expelling as much air from the lungs as possible. Inhale deeply while firmly pressing down on bottle to activate spray mechanism. Try to hold breath a few seconds before exhaling. Walt one full minute if second dose is necessary.

5 Replace mouthpiece and cap on bottle to protect it at all times. Fits into pocket, purse or may be placed on bedside table.

WARNINGS: Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately. Avoid spraying in eyes. Contents under pressure. Do not break or incinerate. Keep MISTOMETER at room temperature. Do not store at temperatures above 120° F or expose to cold. Keep out of reach of children.

NOTE: The idented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlordluorocarbons (CFC's)

This product contains dichlorodifluoromethane and dichlorotetrafluoroethane, substances which harm the environment by destroying ozone in the upper atmosphere. Your physician has determined that this product is likely to help your personal health USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN It you have any questions about alternatives, consult with your physician.